

Subcutaneous palivizumab (Synagis®) administration in an infant with congenital type 2B von Willebrand disease

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Abstract

Intramuscular injections are contra-indicated in infants with either acquired or congenital bleeding disorders. In such patients, it is unlicensed practice to administer vaccines by subcutaneous route. However, there are no reports on subcutaneous administration of palivizumab (Synagis®). We report on the tolerance and effects of subcutaneous palivizumab administration in a former preterm girl with type 2B von Willebrand disease. Repeated subcutaneous injections of palivizumab were well tolerated with minor local reactions and no systemic side effects.

Consequently, we suggest to consider the subcutaneous instead of the intramuscular route in a setting of a valid indication for palivizumab, but a contraindication for intramuscular administration. More importantly, off-label or unlicensed practices should be reported to share and improve pharmacotherapy or at least illustrate knowledge gaps.

Keywords

Palivizumab, pharmacovigilance, subcutaneous, unlicensed practice, type 2B von Willebrand disease.

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Introduction

Infants with bleeding disorders should receive the recommended immunizations for their age group, but should preferably receive the vaccine subcutaneously rather than intramuscularly or intradermally, unless covered – when applicable – by infusion of clotting factor concentrates (level 4 of evidence) [1]. This is because an intramuscular bleeding does not only result in acute pain and impairment, but may also result in muscular fibrosis and permanent dysfunction. Such coagulation disorders can either be congenital (e.g. hemophilia A or B, von Willebrand disease), or acquired (e.g. during anticoagulation). In these cases, there is the unlicensed practice to administer vaccines by subcutaneous route. This practice has been reported for example for hepatitis B vaccination [2]. Despite extensive literature search, we were unable to retrieve any published experience on the use of the subcutaneous route for palivizumab (Synagis®, Abbvie, Wavre, Belgium). Synagis® is labeled for intramuscular injection and the label only suggests that “Synagis® should be given with caution to children with thrombocytopenia or any coagulation disorder” [3].

However, there are a lot of polyclonal and monoclonal antibody formulations that are administered by subcutaneous route. Moreover, pharmacokinetic studies on monoclonal or polyclonal antibodies following either intramuscular or subcutaneous administration reported similar peak and trough values [4]. Further supported by a mathematical description for subcutaneous or intramuscular administration of monoclonal antibodies [5], we decided to administer palivizumab by subcutaneous route (15 mg/kg/month) and to document the effects in a former preterm girl diagnosed with type 2B von Willebrand disease.

Case presentation

The presented case regards a girl that was born as the third child from a mother with known type 2B von Willebrand disease at the gestational age of 34 weeks and a birth weight of 2.4 kg, and subsequently needed respiratory support and additional oxygen in the first week of life. Based on the prolonged activated partial thromboplastin time (aPTT), a reduced von Willebrand factor ristocetine cofactor activity (39%) and thrombocytopenia ($18 \times 10^9/L$), the

diagnosis of type 2B von Willebrand disease was suspected, and subsequently confirmed by genetic testing. Further neonatal stay in the hospital was without additional problems, but she displayed an apparent life threatening event (ALTE) at the age of 2 months (42 weeks of corrected age) at the outpatient clinic. During a diagnostic blood sampling, the infant collapsed with bradycardia, desaturation and hypotonia, and needed basic resuscitation (stimulation, oxygen, bag ventilation). During subsequent admission, gastro-oesophageal reflux was suspected while respiratory syncytial virus (RSV) antigen detection in a nasopharyngeal aspirate at that time was negative. Based on the preterm birth (approved indication for reimbursement in Belgium for preterm neonates < 35 weeks of gestational age, if respiratory support > 48 hours after birth was needed, and if the first 6 months of postnatal life are during the RSV season), and further supported by the ALTE event, we felt that there were good arguments in support of RSV prophylaxis.

Although this is an unlicensed practice not supported by published experience, we felt that subcutaneous administration of palivizumab was appropriate in line with published guidelines [1]. This decision was also based on extrapolation from other polyclonal and monoclonal antibodies [4, 5]. Despite these supporting guidelines, we only retrieved one similar case, however not reported in the public domain. Following contact with the medical advisors of the manufacturer, the company informed us that they had access to one other case report (male former preterm infant, warfarin treatment following thrombosis of the vena cava inferior) treated with subcutaneous palivizumab [6].

The rationale and the available options were discussed with the parents. Following parental consent, we decided to document prospectively the tolerance and effects of subcutaneous palivizumab administration in this former preterm girl. Spare plasma samples (peak and trough levels) were also collected, but analysis was not possible since we had no access to the only valid quantification technique (copyright owned, not readily available). The girl received 5 monthly subcutaneous injections (15 mg/kg, in either the left or right upper leg, weight range 4.6 to 6.6 kg) and was subsequently monitored by a physician (KA) during at least 1 hour for systemic and local side effects with subsequent evaluation of tolerance by the parents. The parents reported that the local tolerance of palivizumab (tenderness,

swelling) was in fact much better when compared to the simultaneously administered (Infarix Hexa®, GlaxoSmithKline Biologicals, Rixensart, Belgium or Prevenar®, Pfizer, Puurs, Belgium, both also subcutaneous) vaccines. She never displayed RSV-related symptoms.

Discussion

We report the first case of repeated subcutaneous administration of Palivizumab in a former pre-term infant with a congenital bleeding disorder. Repeated subcutaneous injection of palivizumab was well tolerated with minor local reactions and no systemic side effects. Consequently, we suggest to consider the subcutaneous instead of the intramuscular route in the setting of a valid indication for palivizumab, but a contraindication for intramuscular administration.

Besides compound specific information, this case report may also serve as an illustration on the need to report more on off-label or unlicensed practices in neonates and infants to share and improve knowledge on pharmacotherapy [7, 8]. Exposure to off-label use or unlicensed practices is not by definition unnecessary exposure without benefit or indication [7, 8]. At present, there are still many effective and reported treatments for neonates that are not included in the drug label. It is very unlikely that there were no other preterm neonates between 1999 and 2014 with either acquired or congenital bleeding disorders with an indication for palivizumab treatment. Since the label suggests that “Synagis® should be given with caution to children with thrombocytopenia or any coagulation disorder” [3], it is up to clinicians to decide what this “caution” covers and to report on the (side-)effects of their decisions. To further illustrate this approach, we refer to the reported practice to consider intravenous palivizumab as a treatment option for persistent RSV infection among immunocompromised pediatric patients: off-label, unlicensed, but of potential benefit in this very specific and extraordinary setting [9].

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Declaration of interest

The Authors declare that there are no conflicts of interest regarding the publication of this paper.

References

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC, Street A; Treatment Guidelines Working Group on Behalf of The World Federation Of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1): e41-7.
2. Miller EJ, Lee CA, Karayiannis P, Holmes S, Thomas HC, Kernoff PB. Immune response of patients with congenital coagulation disorders to hepatitis B vaccine: suboptimal response and human immunodeficiency virus infection. *J Med Virol*. 1989;28(2):96-100.
3. European Medicine Agency, www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000257/WC500056908.pdf, last access: 26 October 2014.
4. Abrahamsen TG, Sandersen H, Bustnes A. Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. *Pediatrics*. 1996;98(6): 1127-31.
5. Zhao L, Ji P, Li Z, Roy P, Sahajwalla CG. The antibody drug absorption following subcutaneous or intramuscular administration and its mathematical description by coupling physiologically based absorption process with the conventional compartment pharmacokinetic model. *J Clin Pharmacol*. 2013;53(3):314-25.
6. Personal communication of dr. Birch K, St. John's Mercy Medical Center, St. Louis, MO, USA, January 25, 1999 to the manufacturer, unpublished.
7. Allegaert K, Langhendries JP, van den Anker JN. Educational paper: do we need neonatal clinical pharmacologists? *Eur J Pediatr*. 2013;172(4):429-35.
8. Stiers JL, Ward RM. Newborns, one of the last therapeutic orphans to be adopted. *JAMA Pediatrics*. 2014;168(2):106-8.
9. Santos RP, Chao J, Nepo AG, Butt S, Stellrecht KA, Pearce JM, Lepow ML. The use of intravenous palivizumab for treatment of persistent RSV infection in children with leukemia. *Pediatrics*. 2012;130(6):e1695-9.